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EXAMINER	
SALMON, KATHERINE D	
ART UNIT	**PAPER NUMBER**
1634	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/601,345	UITTERLINDEN ET AL.	
	Examiner	Art Unit	
	Katherine Salmon	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 July 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *6,8-12,21,24 and 29-33* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *6,8-12,21,24 and 29-33* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. This action is in response to the papers filed 7/13/2006. Currently, Claims 6, 8-12, 21, 24, and 29-33 are pending. Claims 1-5, 7, 13-20, 22-23, and 25-28 have been canceled.

2. The following rejections are applied as necessitated by amendment or are reiterated. Response to arguments follows.

3. This action is FINAL.

Withdrawn Objections

4. The objection to the claims made in Section 5 of the previous office action, is moot in view of the cancellation of the claims.

Withdrawn Rejections

5. The rejections of Claims 12-15 under 35 USC 112/second paragraph, made at section 6 of the previous office action, is moot in view of the amendments of the Claims. Specifically Claims 13-15 have been canceled. Claim 12 has been amended to include a positive process step relating back to the preamble.

6. The rejection of Claims 1-3, 8-10, 12-13, 19-20, and 29-30 under 35 USC 102(b), made at section 9 of the previous office action, is moot in view of the cancelled claims and the amendment to claims drawn to haplotype px, baT.

7. The rejection of Claims 4-5, 14-15, and 26 under 35 USC 103(a) made at section 11 of the previous office action, is moot in view pf the cancellation of the claims.

New Grounds of Rejection Necessitated by Amendment

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. Claims 6, 8-11, 21, 24, 29-31, and 33 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 6, 8-11, and 29-31 recite the limitation "the mammalian subject" in lines 9-10 of Claim 6. There is insufficient antecedent basis for this limitation in the claim. It is suggested that the claim be changed to correct the antecedent basis by amending the claim to "the Caucasian female subject".

Claims 21, 24, and 33 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are the essential steps of formulating a treatment regimen to decrease the risk of bone fracture. The claims do not provide any steps to formulate a treatment regimen via analysis of nucleic acid and therefore there is a gap between the steps.

Claim Rejections - 35 USC § 112- Enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 6, 8-11, 21, 24, 29-31, and 33 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404,

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention

Claim 6 is drawn to a method of determining susceptibility to bone fracture compromising determining the presence of px and baT and the copy number. Claims 8-9 are drawn to a method performed in vitro and on a blood or tissue sample. Claim 10

is drawn to a mammalian subject suffering from low bone mineral density. Claim 11 is drawn to a mammalian subject, which has a normal level of bone mineral density. Claim 21 is drawn to a method of formulating a treatment regimen to decrease the risk of bone fracture in a mammalian subject comprising determining if the px and baT haplotype is present. Claim 24 is drawn to administering a treatment effective to decrease the risk of bone fracture. Claims 29 and 30 are drawn to a method to determine susceptibility of a bone fracture wherein the presences of the haplotype is determined by amplification of a portion of the first intron of the estrogen receptor alpha gene and amplification of the portion of the vitamin D receptor gene between exon 7 and 3' untranslated region. Claim 31 and 33 define the baT allele as homozygous.

The claims are drawn to methods of determining ANY bone susceptibility with heterozygous haplotypes of px, baT. Claim 9 is drawn to a method of sampling ANY subject. The claims are drawn to a method of formulating ANY treatment regime.

The invention is in a class of invention which the CAFC has characterized as "the unpredictable arts such as chemistry and biology." Mycogen Plant Sci., Inc v. Monsanto Co., 243 F.3d 1316, 1330 (Fed. Cir. 2001).

Guidance in the Specification

The specification asserts unexpected associations between specific Estrogen Receptor alpha gene (ERα) and vitamin D receptor (VDR) genotypes and the vertebral fracture (p. 3 lines 9-11). The specification asserts the term "bone damage" does not include low bone mineral density (BMD) (p. 9 lines 20-21). The specification does not

teach how to differentiate fractures associated with BMD and fractures not associated with BMD.

The specification asserts that risk of susceptibility to bone damage is independent of bone mineral density (p. 9 lines 28-30). The specification asserts that there is a correlation between individuals with the p and x alleles and susceptibility to bone fractures (p. 11 lines 8-11). The specification asserts that the p and x alleles are specific polymorphisms in the ERα known as C397T and G351A (p. 11 lines 5-8). The specification asserts a subject having the px haplotype in ERα and a haplotype of BAt or baT for the VDR polymorphisms is susceptible to bone fractures (p. 11 lines 13-14). Bat and baT haplotypes do not appear to distinguish susceptibility.

The specification teaches only the ERα and VDR haplotypes from humans. The specification is silent with regard to the analysis of these haplotypes in other mammalian species. The specification does not teach any correlative polymorphic sequences between human and other mammalian species in regard to these two genes. The specification does not show what the correlative sequence would be in other mammalian sequences. The specification does not indicate that the same haplotype pattern can be observed in other mammalian species.

The specification teaches the preferred method of treatment is prescribing or administering an agent that reduces the susceptibility of a subject to bone fracture (p. 15 lines 15-16). The specification lists examples such as administering sodium alendronate, parathryoid hormone, anabolic steroids, or vitamin D preparations (p. 15 lines 18-20). The specification teaches a method of treating a population, but does not

teach a method of formulating a treatment regimen to decrease the risk of bone fracture. It is unclear if ANY treatment regimen decreases the risk of bone fracture. Further, the steps to formulate a treatment regimen are not provided by the specification. It is unpredictable that ANY formulated treatment regimen would decrease the risk of bone fracture. The specification asserts the method of formulating a treatment regimen to decrease the risk of bone fracture comprises analyzing the nucleic acid molecules to determine the presence of the haplotype (p. 19 lines 1-5). The specification is silent with regard to any other method steps involved in formulating a treatment regimen. It is unpredictable to formulate ANY treatment regiment by analyzing the genotype. The skilled artisan would have to perform undue experimentation in order to provide the necessary steps to formulate a treatment regimen from a genotypic analysis.

Working Examples

The specification provides an example that asserts the polymorphisms in the ERα gene and the VDR gene are positively correlated with increased susceptibility to bone fracture in human beings (p. 23 lines 1-4).

The specification asserts women are grouped according to carrier status for the ER alpha and VDR haplotypes as homozygous carriers (genotype 11) and heterozygous carriers (genotypes 12 and 13) in table 3 (p. 27 lines 12-16). Table 3 lists the p values for lumbar spine BMD and femoral neck BMD (p. 28). The only significant p values are observed in data of the lumbar spine BMD with HOMOZYGOUS VDR haplotype (p value <0.001) and the combination of HOMOZYGOUSE VDR and

HOMOZYGOUS ER alpha haplotypes (p value 0.05) (p. 28 Part A of Table 3).

Quantity of Experimentation

The quantity of experimentation in this area is extremely large since there are a significant number of parameters which would have to be studied. The skilled artisan would have to determine the relationship of the ER alpha (px) and the VDR (baT) haplotype for any type of bone fracture. Further the specification only teaches a statistically significant association between the homozygous baT allele and the combination of the homozygous baT and homozygous px alleles in lumbar spine breaks. The skilled artisan would need to determine if an association can be made in ANY bone fracture breaks. The skilled artisan would also need to determine if the association is based on the homozygous alleles or if an association can be made with the heterozygous alleles of baT. Further, the skilled artisan would need to determine the steps involved with making a treatment regimen based on the genetic testing of baT and px.

This would require a large amount of inventive effort, with each of the many intervening steps, upon effective reduction to practice, not providing any guarantee of success in the succeeding steps.

Level of Skill in the Art

The level of skill in the art is deemed to be high.

Conclusion

In the instant case, as discussed above, in a highly unpredictable art where haplotype and alleles are provided but there is no support in the specification for the use of heterozygous alleles of baT in ANY type of bone fracture. Given there is no support in the specification for determining susceptibility in ANY subject (Claim 9). Given there is no support in the specification for the formulation of the steps of Any treatment regimen. Given the broad claims in an art whose nature is identified as unpredictable, and the large quantity of research required to define these unpredictable variables, the lack of guidance provided in the specification balanced only against the high skill level in the art, it is the position of the examiner that it would require undue experimentation for one of skill in the art to perform the method of the claim as broadly written.

Response to Arguments

The response traverses the rejection. (A) The response asserts the claims have been amended to limit to detecting bone fracture susceptibility in Caucasian female subjects (p. 8 last paragraph). (B) The response asserts that even though the highest association with fracture risk was when the baT was homozygous the combination of px and baT heterozygotes carry a higher risk compared to the non-baT genotype (p. 9 1st paragraph). These arguments have been reviewed but are not found persuasive.

(A) Though the independent claims have limited the scope to Caucasian female, the dependent claim 9 is not limited in scope. Claim 9 is drawn to performing the method on ANY subject. To correct the scope of Claim 9 it is suggested that Claim 9 be amended to "the Caucasian female subject".

(B) The specification asserts a significantly statistically significant p value in a population wherein there is at least one allele with px and a homozygous haplotype of baT (Table 3). The reply asserts that heterozygotes of baT show a risk of fracture (p. 9 of reply; p. 30 lines 11-17 and Figure 4 of the specification). Figure 4 only shows a significantly significant association of the combination of ER alpha homozygote and a VDR homozygote. According to Figure 4 there is no other significant association of bone fracture and the ER alpha and VDR. Further, the reply asserts that heterozygous baT is associated with increased fracture risk, pointing to p. 30 lines 11-17 of the specification. Uitterlinden et al. (Journal of Bone and mineral Research Vol 16 2001) (the previous study which is presented on p. 30 lines 11-17) is a study of susceptibility of bone fracture according to the VDR haplotype and the COLIA1 genotype (p. 382 Table 3 of Uitterlinden et al). The population of Uitterlinden et al. does not define itself by px and baT therefore it is unpredictable that the same correlation of the VDR haplotype and the COLIA1 genotype can be made in a population of ER alpha and VDR. The claims are drawn to a population defined by BOTH ER alpha and VDR.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

10. Claims 12 and 32 are rejected under 35 U.S.C. 102(b) as being anticipated by Warrell J. et al. (US Patent 4,529,593 July 16, 1985).

With regard to Claims 12 and 32, Warrell J. et al. teaches a method of treating bone fractures in a human individual comprising administering an effective amount of a pharmaceutically acceptable gallium compound (Abstract and Claim 24). Warrell et al. teaches that all patients responded to the treatment by a reduction in serum calcium concentration to normal values (Column 7, lines 40-45)Warrell J. et al. teaches a method of applying to ANY human individual a treatment to reduce bone fractures. A population of ANY human individual would include individuals with genotypes px and baT. Therefore, individuals with px and baT are encompassed by the method of Warrell J. et al.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

11. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was

not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Though the claims are rejected above as not being enabled the following 103 rejections are being made in the interest of compact prosecution of the application.

12. Claims 6, 9-11, and 29-31 are rejected under 35 U.S.C. 103(a) as being unpatentable over Willing et al. (Journal of bone and mineral research 1998 Vol 13, p. 695) in view of Uitterlinden et al (Journal of bone and mineral research 2001 Vol. 16 p. 379).

With regard to Claim 6, Willing et al teaches that there was an association between Caucasian women who were homozygous ppxx and lumbar spine and total body BMD levels (Abstract and Table 4). Willing et al teaches that low bone mineral density is a risk factor for osteoporosis and related fractures (Introduction 1st paragraph). Willing et al teaches the BsmI restriction site was analyzed (Vitamin D Receptor p. 697). With regard to determining the copy number, the specification does not provide an explicit definition of "copy number". The instant specification describes grouping subjects by allele copy number (0, 1, 2) (p. 25 lines 4-5). The courts have stated that claims must be given their broadest reasonable interpretation consistent with the specification *in re Morris* , 127 F.3d 1048, 1054-55, 44 USPQ2d 1023, 1027-28 (Fed. Cir. 1997); *In re Prater*, 415 F.2d 1393, 1404-05, 162 USPQ 541, 550-551 (CCPA

1969); and *in re Zletz*, 893 F.2d 319, 321-22, 13 USPQ2d 1320, 1322 (Fed. Cir. 1989) (see MPEP 2111). The claims are given the broadest reasonable interpretation consistent with the indefinite claim language and specification wherein the "copy number" can be interpreted broadly as the number of molecules of a particular type in a cell. Willing et al. teaches determining if the individual is homozygous or heterozygous (determining if the copy number is 1 or 2) for p, x, and b (Table 4 and Table 5).

With regard to Claim 9, blood samples were used to perform the genotyping method (p. 696 1st column Subjects last full paragraph). With regard to Claim 10 and 11, Wiling et al. teaches a method of testing normal and low BMD (p. 701).

With regard to Claim 29, Willing et al. teaches primers designed to amplify the intragenic polymorphic PvuII and XbaI sites followed by restriction digestion (p. 697 column 1 last sentence and p. 698 1st column 1st full paragraph).

Willing et al, however, does not teach the use of the vitamin D receptor gene sites of ApaI and TaqI.

Uitterlinden et al. teaches the interaction between VDR and susceptibility for fracture. With regard to Claim 6, Uitterlinden et al teaches that in a study of the Rotterdam population the baT haplotype was overrepresented among fracture cases and can be used as a genetic marker for osteoporotic fracture in women independent of BMD (p. 380 Study subjects and Abstract). Uitterlinden et al. teaches determining if a woman is homozygous of heterozygous for the VDR haplotype (bat) (Table 3).

With regard to Claim 30, Uitterlinden et al teaches a method of amplifying the vitamin D receptor by polymorphic restriction enzyme recognition sites at the 3' end of

the VDR gene (p. 381 1st column 1st paragraph). With regard to Claim 31, Uitterlinden et al. teaches a method wherein the subject is homozygous for the baT allele haplotype (Table 3).

Therefore it would have been prime facie obvious to one of ordinary skill in the art at the time the invention was made to modify the method of Willing et al. to further include ApaI and TaqI as taught by Uitterlinden et al. The ordinary artisan would have been motivated to improve the method of Willing et al. to include ApaI and TaqI taught by Uitterlinden et al. because Uitterlinden et al. teaches analyzing only the BsmI can compromise the outcome of studies because heterogeneous groups are compared. Uitterlinden et al. teaches the extensive linkage disequilibrium at the 3' end of VDR gene, can be measured accurately by the molecular haplotyping of three RFLPs, BsmI, ApaI, and TaqI. Uitterlinden et al. teaches the haplotypes, which by themselves are not functional polymorphisms, can be used as markers for truly functional polymorphisms elsewhere in the 3' end of the VDR gene (p. 383 1st column 1st paragraph).

Response to Arguments

The response traverses the rejection. (A) The response asserts Willing et al. does not teach or suggest analysis of the ApaI and TaqI polymorphisms of the VDR gene (p. 11 2nd paragraph) (B) The response asserts that Willing et al. does not teach determining copy number (p. 11 2nd paragraph). These arguments have been reviewed but are not found persuasive.

(A) The rejections of the claims under 102(b) have been withdrawn because of the amendments to the claims. The newly amended claims are rejecting as being

obvious over Willing et al. in view of Uitterlinden et al. Though Wiling et al. does not teach analysis of the ApaI and TaqI polymorphisms of the VDR, Uitterlinden et al. does and teaches that the combination of bat is needed to determine bone susceptibility. Therefore the skilled artisan would be motivated to test BsrI as taught by Wiling et al. in combination with ApaI and TaqI as taught by Uitterlinden et al.

(B) The specification provides no precise definition of "copy number". Willing et al. and Uitterlinden et al. both teaches determining if a patient is homozygous or heterozygous for specific haplotypes. The term "copy number" can be broadly interpreted as determining the homozygous or heterozygous genotype of an individual.

Conclusion

13. No claims allowed.

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Katherine Salmon whose telephone number is (571) 272-3316. The examiner can normally be reached on Monday-Friday 8AM-430PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on (571) 272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Katherine Salmon

Katherine Salmon
Examiner
Art Unit 1634

BJ FORMAN, PH.D.
PRIMARY EXAMINER